

REMARKS

This Amendment is in response to the Official Action mailed February 26, 2003.

Claims 23-30 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. The Examiner has alleged that the instant specification fails to allow the skilled artisan to practice the invention without undue experimentation. Applicants respectfully traverse this rejection for the reasons set forth hereinafter.

The Examiner contends that the specification does not provide enablement for specific methods of making hollow nanoparticles by "burning off the polymeric material." The Examiner's position in this regard is based solely on speculation, and in fact requires one to disregard the entire specification hereof. In that specification, in the paragraph bridging pages 16 and 17, the preparation of hollow magnetic particles is described. It is specifically noted therein that the inner nuclei made of polymeric metal chelating agent can be burned off in an inert atmosphere, and that in a preferred embodiment this is performed at a temperature preferably from 500 to 900°C.

It is clear from this disclosure alone that one of ordinary skill in this art would have no difficulty carrying out this operation, and it is quite obvious that the polymeric material would be burned off at these temperatures. Indeed, since the burning step is carried out in an inert atmosphere, the inorganic component of these metal particles will not be affected, resulting in a nanoparticle which is only modified by lacking the polymeric component. This, however, is not where

the present disclosure leads. To the contrary, in Example 17 on page 32 of the specification, there is a specific example of the burning off of hollow magnetized nanoparticles. It is difficult to see how any more disclosure could be provided to enable one of ordinary skill in this art to carry out this procedure.

The rest of the Examiner's rejection in this regard is pure speculation. The Examiner thus questions some alleged failure to describe the functional correlation between the burned-off metal particles and those which do not undergo the step comprising burning the polymeric material by a device producing high temperatures. There is simply no basis for the Examiner's position in this regard.

The Examiner goes on to raise further unsupported questions about the disclosure. The fact of the matter is, however, that none of this relates to the alleged deficiency of enablement under § 112. The specific claimed process is fully enabled, and anyone of ordinary skill in this art could readily carry it out by reading this disclosure alone. It is therefore respectfully requested that this rejection be eliminated.

Claims 19, 20 and 30 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended these claims to more specifically point out and distinctly claim the subject matter which applicant regards as the invention. Accordingly, entry of the amendment is respectfully requested.

Likewise, claims 1 and 25 have been amended in response to the Examiner's objections. Accordingly, entry of the amendment is respectfully requested.

Claims 1-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Siiman et al.*, *Ugelstad et al.*, or

Margel et al. in view of *Remington*, *Callewaert et al.* and *Vasconcelos et al.* The Examiner contends that the three primary references disclose all of the limitations of the claimed invention except successively repeating the steps d) to f) of claim 1, and that the final step of claim 1, step g), encompasses conventional titration assay employed in the art of analytical chemistry and is taught by the three secondary references. The Examiner concludes that it would have been obvious to employ the titration methods of the secondary references and add the metallic solutions of the primary references in dropwise fashion because such titration method is conventionally used in the art to assess the maximum complexation between a polymeric moiety and a metallic ion. This rejection is respectfully traversed in view of the above amendments and for the reasons set forth below.

Applicants respectfully submit that the combining of these various references in an attempt to reject the present claims is based at least in part on a misunderstanding of the nature and substance of the present invention. In accordance with this invention, the applicants have discovered a novel method for producing a novel product; namely, magnetic nanoparticles which have characteristics that have been unobtainable to date. These include greater uniformity and smaller particle sizes than those which has been previously achieved. This is achieved in accordance with the present invention by a specific claimed method which is nowhere suggested by the prior art. Indeed, the Examiner essentially admits this.

The claimed invention hereof permits the production of a unique product by a specific claimed sequence of steps in which an aqueous solution containing a soluble polymeric metal chelating agent is contacted with metal salts including metal

ions capable of forming oxides which are magnetic, and particularly in amounts which do not exceed substantially the binding capacity of the chelating agent. The following steps of claim 1 require presenting the metal ions in appropriate oxidation states, maintaining pH's of at least 7, introducing additional amounts of metal salts, again present in the required oxidation states in order to be magnetic, further maintenance of the pH, and sequential operation in order to obtain mono-dispersed nanoparticles coated with magnetic metal oxide. None of the prior art produces this result, much less teaches this specific method. Indeed, the Examiner appears to have ignored the entire specification, including examples in this case which vividly demonstrate the significance of this invention as compared, for example, to a similar process in which, instead of the stepwise additions required by the claims, there is a single addition of material, with demonstrably inferior results (as seen, for example, in Examples 2 and 3 and Tables 1 and 2 hereof). When it is realized that the Examiner's entire position with respect to alleged obviousness in this case amounts to an admission that the prior art does not teach this process, and in which the Examiner blithely takes the position that the claims encompass conventional titration assays employed in analytical chemistry, it can be seen that there is absolutely no basis for the rejection which has been interposed in this case.

Turning first to the *Ugelstad et al.* reference, viewed in its best possible light, this reference discloses methods of preparing porous magnetic particles in which polymer particles are prepared and provided with active radicals, except where they are porous particles, in contact with a mixture of iron salts so as to prepare particles having magnetic oxides on the surface as well as in the body of these particles. The process

is not the process of the presently claimed invention, and the product is far inferior thereto. The best interpretation of *Ugelstad et al.* which the Examiner can make is that it is comparable to the comparative products shown in Examples 2-4 herein in which the ingredients are combined in a single step. In that case, the products obtained have been shown to be highly inferior to the products obtainable in accordance with the present invention.

Indeed, the Examiner admits that *Ugelstad et al.* fails to teach repetition of steps d) through f) of claim 1, as is allegedly the case with each of the other primary references relied upon by the Examiner (see, discussion below). The Examiner attempts to overcome this admitted deficiency by reference to three secondary references which however, have nothing whatsoever to do with the subject matter of this invention. *Remington*, *Callewaert et al.* and *Vasconelos et al.* are cited as collectively showing titration methodologies known in the art. These references are used for the general purposes of determining concentrations of acids or bases, for "potentiometric titration" for analytically assessing the degree of precipitation or complexation in solutions, or for the use of potentiometric titration to demonstrate the affinity of various metals to natural or synthetic polymers for various reasons.

Firstly, the specific steps of claim 1 are not conventional titration assays, but require the repeat of a series of substantive steps of the claimed process which are crucial in obtaining these unexpected results, as mentioned above and as set forth in the specification and Examples herein. Steps d) through f) in these claims are necessary for successive repetition as many times as is required in order to obtain mono-dispersed nanoparticles coated with magnetic metal oxide. How one could convert standard titration procedures, or

"potentiometric titration" to such claims is unimaginable. Titration methods are those for determining the concentration of substances in solution by the addition of standard solutions until the reaction between it and the solute is complete. The completion of such reaction is often signaled by an indicator or, as shown, for example, in *Callewaert*, by the point in the curve of pH versus the addition of the standard solution at which the pH increases most rapidly. In the steps in claim 1, however, no concentration is determined in any of these steps, and no standard solutions are used. The Examiner's attempt to overcome the admitted deficiencies of these primary references, particularly in view of the data submitted in this application and highlighted above, is without effect.

Turning to the other cited primary references, they are even less effective than is *Ugelstad et al.*

Siiman et al. discloses methods for preparing uniform colloidal magnetic particles from a solution and then coating them with a polymer which acts as a reductant for the metal salt. *Siiman et al.* thus discloses a one-step process for preparing coated colloidal metal(O) particles by heating aqueous solutions of a metal salt with an amino-derivitized polysaccharide with at least one reducible sugar component to reduce the metal salt to a metal(O) particle or simultaneously coating the particle with the polysaccharide. There is no suggestion in *Siiman et al.* of magnetic metal oxides, nor of controlling the oxidation state to form an oxide that is magnetic. The Examiner thus attempts to overcome this clear deficiency of *Siiman et al.* by stating that the metal salt can be FeSO_4 while maintaining the metal in its oxidation state in the presence of KNO_3 . However, the fact is that the metals disclosed therein are noble metals specified in column 6, lines 15-20, including gold, silver, rhodium, platinum,

palladium and iridium. Finally, far from being maintained in its oxidation state, the metal salt in this case is, in fact, reduced (see, column 3, lines 33-35). It is therefore clear that the *Siiman et al.* reference is, if anything, even inferior to *Ugelstad et al.* Far from teaching the preparation of a product which includes mono-dispersed nanoparticles coated with magnetic metal oxide, *Siiman et al.* teaches a different method of preparing metal particles coated with an organic compound. There is simply no suggestion of the presently claimed process therein.

Finally, the Examiner also attempts to rely on *Margel et al.* as a primary reference. This patent is at least as irrelevant as those discussed above. In *Margel et al.*, polyacrolein-type microspheres are produced for various biological uses. This patent is principally directed to methods of preparing these polyacrolein microspheres, and does not generally relate to preparing nanoparticles coated with magnetic metal oxides. The Examiner, however, refers to Example 3 of *Margel et al.*, which relates to the preparation of magnetic microspheres in which the polyacrolein microspheres are produced in the presence of a ferrofluidic solution, which is an aqueous dispersion of Fe_3O_4 specified therein. There is, of course, no oxidizing agent present in Example 3, but in any event the product produced by *Margel et al.* certainly does not constitute a nanoparticle having a magnetic metal oxide coating thereon, and in any event there is admittedly no disclosure of the specific method set forth in claim 1 herein.

With respect to the overall nature of this rejection, applicant respectfully submits that each of the primary references utterly fails to suggest the specific method of claim 1, nor any method for obtaining the unique products of this invention. Furthermore, the secondary references relate to

conventional titration, which is not the subject of this invention, and in any event there is no motivation whatsoever to combine the teachings of these references, since the secondary references have nothing to do with the production of nanoparticles coated with magnetic metal oxides or anything of the sort.

Ignoring all of the above, however, and even if one assumes that everything the Examiner says about the primary references is true, the necessary admission of the utter failure of the art to teach the specific sequence of repeating steps required by claim 1 must be fatal to this rejection. This is not only in view of the differences between the present claims and the prior art, but in view of the impressive evidence set forth in the specification, such as in Examples 2 and 3, in which direct comparisons are made between the results of single and stepwise dose additions of ferrous salts, providing Fe^{+2} ions which form an Fe^{+3} ions by oxidation. With the claimed stepwise addition, "the magnetized nanoparticles were well dispersed and did not settle even during several months, whereas those formed by the single addition were broad size distribution and contained a high percentage of agglomerated particles." Certainly, nothing in the prior art would suggest that a stepwise addition of the iron salts would greatly improve on a single addition such as that of the art as interpreted by the Examiner. This alone establishes the patentable nature of the invention.

It is therefore respectfully submitted that all of the claims in this application now possess the requisite novelty, utility and unobviousness to warrant their immediate allowance, and such action is therefore respectfully solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is

Application No.: 09/701,210

Docket No.: LUZZATTO 3.3-051 CIP

respectfully requested that he telephone applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: August 26, 2003

Respectfully submitted,

By

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